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ORIGINAL ARTICLE

Male–female differences in quality of life and coping style in patients with Marfan syndrome and hereditary thoracic aortic diseases

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Abstract

Hereditary thoracic aortic diseases (HTAD) such as Marfan syndrome (MFS) affect multiple organ systems and provide a risk of acute aortic dissection, which causes lifelong uncertainties. Although health-related quality of life (HRQOL) was found to be reduced in HTAD patients, no studies have evaluated male–female-specific aspects of HRQOL and coping in this population. This study aims to evaluate HRQOL in HTAD patients compared to the general population; assess male–female differences in HRQOL and factors associated with HRQOL; evaluate coping styles in male and female HTAD patients and identify factors associated with acceptance. All consecutive adult patients who visited the specialized HTAD outpatient clinic between 2013 and 2018 were asked to complete three HRQOL questionnaires: the Short Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS), and the Nijmegen Clinical Screening Instrument (NCSI). In total, 142 patients were included (mean age 42.1 years, 65 females, 123 MFS). Compared to the general population, HTAD patients scored significantly lower on multiple SF-36 sub-domains (males: General Health 54.5 ± 18.8 vs. 71.6 ± 20.6 , $p < .001$; Vitality 58.3 ± 20.4 vs. 71.9 ± 18.3 , $p < .001$; females: Physical Functioning 67.5 ± 23.8 vs. 80.4 ± 24.2 , $p = .003$; Role Physical 58.3 ± 45.1 vs. 73.8 ± 38.5 , $p = .047$; General Health 49.4 ± 24.3 vs. 69.9 ± 20.6 , $p < .001$; Social Functioning 73.5 ± 22.0 vs. 82.0 ± 23.5 , $p = .027$). Females scored significantly lower than males on the SF-36 physical component score (41.6 [IQR 35.5 – 53.1] vs. 49.3 [IQR 42.3 – 54.6], $p = .035$). Males scored significantly higher on the coping style denial than females (2.75 [IQR 2.00 – 3.25] vs. 2.25 [IQR 1.75 – 3.25], $p = .018$). High scores on acceptance were found in 38 (26.8%) of HTAD patients, and these patients showed significantly better scores on the NCSI, SF-36, and HADS, except on NCSI Satisfaction Relationships and SF-36 Physical Functioning and Mental Health. Acceptance was associated with more medication use (beta blocker use, $p = .008$; angiotensin receptor blocker use, $p = .003$) and less hypertension ($p = .001$).

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In patients with MFS, employment was strongly associated with better scores on the NCSI. In conclusion, HTAD patients showed subnormal HRQOL, especially females. Interestingly, in both males and females factors such as employment, coping style, and disease acceptance seem more important for HRQOL than disease-related factors. This highlights the importance of genetic counseling and guidance for HTAD patients, and offers valuable leads for HRQOL improvement.

KEYWORDS

distress, genetic counseling, health-related quality of life, Marfan syndrome, mental health, psychosocial, sex

1 | INTRODUCTION

The incidence of thoracic aortic diseases including thoracic aortic aneurysms and dissections has been increasing and is currently estimated to be about 9 per 100,000 per year in women, and 16 per 100,000 per year in men (Olsson, Thelin, Stahle, Ekblom, & Granath, 2006). In over 20 percent of cases, there is an inherited pattern for thoracic aortic aneurysms (Albornoz et al., 2006), and often multiple family members are affected. Patients with these hereditary thoracic aortic diseases (HTAD), such as Marfan syndrome (MFS), often experience multiple serious complaints during their lifetime, which are mostly due to skeletal, ocular, or cardiovascular manifestations. On top of that, these patients are at risk of acute aortic dissection (Murdoch, Walker, Halpern, Kuzma, & McKusick, 1972). Therefore, HTAD patients with or without aortic involvement face many uncertainties and require lifetime medical surveillance, lifestyle alterations, pharmaceutical treatment, and often surgical procedures.

Evidence of the effects of living with this potentially life-threatening inheritable disease on health-related quality of life (HRQOL) is scarce. So far, it has been shown that HTAD patients have a lower HRQOL compared to the general population and comparable to other chronic diseases (Goldfinger et al., 2017; Olsson & Franco-Cereceda, 2013). Physical aspects seem affected rather than mental well-being (Olsson & Franco-Cereceda, 2013; Rand-Hendriksen et al., 2010). Moon et al. showed that apart from disease-related factors, there are other important factors which influence HRQOL in MFS patients, such as social support (e.g. family/friends support) and bio-behavioral factors (e.g. anxiety, depression, fatigue, pain; Moon, Cho, Huh, Kang, & Kim, 2016). Even though evidence on HRQOL in HTAD patients, and MFS patients in particular, is gradually increasing, guidelines on current clinical practice do not yet include any HRQOL assessment, psychosocial assessment, or psychological counseling (Erbel et al., 2014; Hiratzka et al., 2010).

Better insight into HRQOL in HTAD patients could help guide genetic counseling, help to explain the relevance of HRQOL to our patients, and aid the creation of intervention strategies for improving HRQOL in this population. In particular, it is important to know in which specific subgroups of HTAD patients HRQOL is most impaired, in order to increase clinician awareness of HRQOL impairment and coping problems in these patients. However, patient-specific

evidence is lacking. Even though HRQOL is known to be different in men and women both in the general population and in specific patient groups (Angst et al., 2002; Norris et al., 2008), no studies have evaluated male–female-specific aspects of HRQOL in this population. Furthermore, very little is known about coping strategies and disease acceptance in HTAD patients, while the latter is known to be an important patient-related factor contributing to patients' adherence to long-term treatments (Connors, Jeremy, Fisher, Sharpe, & Juraskova, 2015; Jankowska-Polanska, Blicharska, Uchmanowicz, & Morisky, 2016). Therefore this study aims to (a) Evaluate male–female-specific HRQOL in HTAD patients compared to the general population, (b) Assess male–female differences in HRQOL and identify male–female-specific factors associated with HRQOL, and (c) Evaluate coping styles in male and female HTAD patients and identify factors associated with the coping style acceptance.

2 | METHODS

2.1 | Participants

All consecutive adult patients (≥ 18 years old) who visited the specialized HTAD outpatient clinic at the Radboud University Medical Center in Nijmegen between 2013 and 2018 were asked to fill-out three quality of life questionnaires: the Short Form 36 (SF-36), the Hospital Anxiety and Depression Scale (HADS), and the Nijmegen Clinical Screening Instrument (NCSI). The HTAD outpatient clinic is a multidisciplinary clinic in which patients are seen by cardiologists, nurse practitioners, or clinical geneticists over the course of annual visits. Questionnaires were distributed directly after an outpatient clinic visit, which was a cardiovascular follow-up visit with their cardiologist or nurse specialist. If patients completed the questionnaires multiple times, only the first measurements were used, in order to avoid bias created by counseling sessions at the HTAD outpatient clinic. Exclusion criteria were related to inability to complete the online surveys, such as a language barrier, intellectual disability, no access to a computer or email address, or unwillingness to complete the questionnaires. The questionnaires were primarily used in clinical practice for patients visiting the HTAD outpatient

clinic of our tertiary care center, in order to assess overall mental and physical health status and to develop patient-specific treatment goals for counseling if necessary. Additional data were collected from the patient files using a standardized case report form shown in Supporting Information S1. Only information collected within 3 months from the date of completion of the questionnaires was used. Diagnosis of MFS was defined as fulfillment of the criteria of the revised Ghent nosology (Loeys et al., 2010). This study was approved by the local ethics committee (ethics committee of the Radboud University Nijmegen Medical Centre, file number: 2019–5451) and was designed, performed, and controlled in accordance with current local and international good clinical practice guidelines (De Nederlandse Gedragscode Wetenschapsbeoefening, 2014; The European Code of Conduct for Research Integrity Revised Edition, 2017; WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2013).

2.2 | Questionnaires

The SF-36 questionnaire is a widely used HRQOL questionnaire with 36 items, which comprises eight domains: Physical Functioning (PF), Role limitations due to Physical health problems (RP), Bodily Pain (BP), General Health perceptions (GH), Vitality (VT), Social Functioning (SF), Role limitations due to Emotional problems (RE), and general Mental Health (psychological distress; MH; Aaronson et al., 1998; Ware Jr. & Sherbourne, 1992). The first four domains (PF, RP, BP & GH) comprise the Physical Component Summary (PCS), and the last four domains (VT, SF, RE & MH) comprise the Mental Component Summary (MCS). All SF-36 sub-domains have a score range of 0–100, with higher scores reflecting a better quality of life. The SF-36 has been translated and validated in the Dutch language, and norm scores of the general Dutch population are available (Aaronson et al., 1998). Male and female scores of HTAD patients on the eight sub-domains of the SF-36 were compared to male–female-specific norm values (Aaronson et al., 1998). Unfortunately, no age-specific norm values are available for males and females separately; additional age-matching was therefore not possible (Aaronson et al., 1998). Male–female-specific PCS and MCS scores were calculated using the mean and standard deviations from the general Dutch population. SF-36 scores of patients who previously underwent aortic surgery were compared to patients who had not undergone aortic surgery, and patients who experienced previous aortic dissection were compared to those who did not.

The HADS is a commonly used questionnaire to assess signs of anxiety and depression. This 14-item scale is divided in two dimensions: anxiety (seven items) and depression (seven items). The responses result in a score for each dimension with a score range of 0–21 and a total overall score range of 0–42. Higher scores represent higher levels of anxiety and depression. The HADS was validated in the Dutch language (Spinoven et al., 1997). A score of 8+ on the HADS anxiety and depression subscales was defined as elevated, since this cutoff point was found to be the most optimal (Bjelland, Dahl, Haug, & Neckelmann, 2002).

The NCSI contains 49 questions and was designed to assess the overall health status of patients, identifying patient-specific treatment goals in order to facilitate behavioral changes (Peters et al., 2009). The NCSI has eight sub-domains: General Quality Of Life; Health-Related Quality of Life; Satisfaction with Relationships; Subjective Impairments; Behavioral Impairments; Subjective Symptoms; Emotions about Symptoms; and Fatigue. Each of the eight sub-domains has its own specific score range as shown in Table 3, with higher scores reflecting more problems on the sub-domain. Therefore, lower scores on the NCSI sub-domains reflect a better quality of life. Additionally, the NCSI includes the ADIQ questionnaire as a measure of coping style, which is based on the stages of grief by Kübler-Ross (1970), which shows resemblances with the stages of disease acceptance: denial, resistance, sorrow, and acceptance. For assessment of each stage, there are three to four questions (Boer et al., 2014). Scores on every stage are transformed to a score range of 1–4, with higher scores reflecting better agreement of this stage with the coping style used by the patient. High scores on the ADIQ stages were defined as a score of 3+. Scores on the ADIQ were compared between males and females for each coping style. Both the NCSI and ADIQ were originally designed and validated in patients with chronic obstructive pulmonary disease (Boer et al., 2014; Peters et al., 2009), and were used thereafter in patients with Q-fever and asthma (Peters et al., 2014; van Loenhout et al., 2013). Unfortunately, norm scores for the general Dutch population are not available; therefore, the NCSI could not be used to compare HTAD patients to the general population.

2.3 | Data analysis

Data were analyzed using SPSS statistics (IBM SPSS Statistics version 25). Continuous data were presented as mean and standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when skewed. Categorical data were presented as frequencies with percentages. Students *t* test or non-parametric Wilcoxon test were used to compare continuous variables, and chi-squared test was used to compare categorical variables. The one-sample student's *t* test was used to compare SF-36 norm values to the study population means. For the patients with MFS, baseline variables that showed a significant association with scores on one of the NCSI sub-domains ($p < .05$) in univariate analysis were included in a multifactor analysis of variance to identify those strongly associated with scores on this sub-domain. A *p*-value of $<.05$ was considered significant.

3 | RESULTS

In total, 142 HTAD patients (65 females) completed one or more questionnaires. All 142 patients completed the NCSI questionnaire, 76 patients (36 females) subsequently completed the SF-36 questionnaire, and 113 patients (49 females) completed the HADS.

Baseline characteristics (shown in Table 1) were compared between males and females; patients who completed the SF-36 and those who did not; and patients who completed the HADS and those who did not. Males had a significantly larger aortic root diameter compared to females ($p = .001$), although the aortic root Z-scores were not significantly different ($p = .635$). Patients who completed the SF-36 had a significantly larger aortic root diameter (41.5 ± 5.3 mm vs. 38.6 ± 5.3 mm, $p = .006$), and aortic root Z-score (3.2 [IQR 1.9–4.8] vs. 2.2 [IQR 1.2–3.5], $p = .004$) than those who did not. Patients who completed the HADS questionnaire had significantly larger aortic diameters than those who did not (40.7 ± 5.4 mm vs. 38.2 ± 5.6 mm, $p = .042$). However, the aortic root Z-score was not significantly different ($p = .135$). There was no significant difference between the percentage of males and females who completed the SF-36 (52.6% vs. 47.4%, $p = .682$) and the HADS (56.6% vs. 43.4%, $p = .255$). A large proportion of our cohort (123/142 patients) was diagnosed with

MFS. Therefore, we additionally compared patients with diagnosis of MFS to patients without MFS, as is shown in Supporting Information S2. Patients with MFS were significantly younger (41.0 ± 14.3 vs. 49.2 ± 16.3 , $p = .023$). The remaining patients were diagnosed with Loeys-Dietz syndrome ($n = 8$), ACTA2 mutation ($n = 1$), and other genetic mutations ($n = 5$), or had no established genetic mutation but did have a thoracic aortic aneurysm and positive family history of aortic disease.

3.1 | HRQOL in HTAD patients

Table 2 shows the SF-36 scores of male and female HTAD patients compared to male and female norm scores of the general Dutch population (Aronson et al., 1998). Overall, male and female HTAD patients both showed lower scores than the general population on most

TABLE 1 Baseline characteristics

	Total (n = 142)	Males (n = 77)	Females (n = 65)	p-value
Age – years	42.1 ± 14.8	42.1 ± 14.9	42.1 ± 14.8	.977
BMI – kg/m ²	23.5 ± 4.5	24.2 ± 4.7	22.7 ± 4.2	.059
Hypertension	17 (12.0)	9 (11.7)	8 (12.3)	.910
Hyperlipidemia	16 (11.3)	11 (14.3)	5 (7.7)	.216
Current smoker	17 (12.9)	8 (11.0)	9 (15.3)	.464
Renal dysfunction	2 (1.8)	0 (0)	2 (4.2)	.097
Beta blocker use	92 (64.8)	55 (71.4)	37 (56.9)	.071
ARB use	59 (41.5)	34 (44.2)	25 (38.5)	.493
Aortic root diameter – mm	40.1 ± 5.5	41.8 ± 5.0	38.4 ± 5.5	.001
Z-score	2.7 ± 2.0	2.6 ± 2.0	2.8 ± 2.1	.635
Abdominal aortic aneurysm	18 (12.9)	12 (16.0)	6 (9.4)	.246
Normal LVEF	135 (96.4)	72 (94.7)	63 (98.4)	.240
Previous surgery	46 (32.4)	28 (36.4)	18 (27.7)	.271
Previous dissection	21 (14.8)	13 (16.9)	8 (12.3)	.444
Diagnosis				.317
Marfan syndrome	123 (86.6)	66 (85.7)	57 (87.7)	
Loeys-Dietz syndrome	8 (5.6)	4 (5.2)	4 (6.2)	
ACTA2 mutation	1 (0.7)	0 (0.0)	1 (1.5)	
Other	5 (3.5)	2 (2.6)	3 (4.6)	
None	5 (3.5)	5 (6.5)	0 (0.0)	.730
Positive systemic score > 7	41 (28.9)	25 (32.5)	16 (24.6)	.304
Positive family history MFS	80 (62.5)	44 (65.7)	36 (59.0)	.437
Current partner	85 (68.5)	48 (71.6)	37 (64.9)	.421
Current work ^a	88 (66.2)	42 (72.4)	27 (62.8)	.304

Note: Data are expressed as $M \pm SD$ or as absolute and percentage.

Abbreviations: HTAD, hereditary thoracic aortic disease; BMI, body mass index; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; MFS, Marfan syndrome.

^aOnly working age (25–65 years) $n = 107$.

SF-36 sub-domains. In females, however, scores were significantly lower in HTAD patients compared to the general population for: Physical Functioning (67.5 ± 23.8 vs. 80.4 ± 24.2 , $p = .003$), General Health (49.4 ± 24.3 vs. 69.9 ± 20.6 , $p < .001$), Social Functioning (73.5 ± 22.0 vs. 82.0 ± 23.5 , $p = .027$), and Role Physical (58.3 ± 45.1 vs. 73.8 ± 38.5 , $p = .047$). Males showed significantly lower scores compared to the general population for: General Health (54.5 ± 18.8 vs. 71.6 ± 20.6 , $p < .001$) and Vitality (58.3 ± 20.4 vs. 71.9 ± 18.3 , $p < .001$).

3.2 | HRQOL in males versus females

Table 3 shows male–female-specific scores on all sub-domains of the three HRQOL questionnaires. On the SF-36 questionnaire, females scored lower on most sub-domains, with a significantly lower score on Physical Functioning (90.0 [IQR 70.0 – 95.0] vs. 75.0 [IQR 55.0 – 83.8], $p = .005$) and on the Physical Component Summary (47.8 ± 9.1 vs. 43.0 ± 10.6 , $p = .035$) but not on the Mental Component Summary (50.5 [IQR 44.4 – 55.5] vs. 52.4 [IQR 44.5 – 56.2], $p = .411$). On the HADS questionnaire no significant differences were seen between sub-scores of males and females. Of females, 18/49 (36.7%) demonstrated elevated scores on the HADS anxiety sub-domain versus 18/64 (28.1%) of males ($p = .330$). On depression 9/49 (18.4%) of females showed elevated scores versus 14/64 (21.9%) of males ($p = .646$). On the NCSI females scored significantly higher than males on the sub-domain Behavioral Impairments (8.8 [IQR 0.0 – 19.3] vs. 0.0 [IQR 0.0 – 11.0], $p = .013$), reflecting a lower quality of life on this sub-domain.

Additionally, HTAD patients rated their overall quality of life on a 0–10 scale; the mean rate in both males and females was 7.3.

3.3 | Previous aortic complications

SF-36 scores of patients, who previously underwent aortic surgery (22/76) or had an aortic dissection (10/76), were compared to patients who did not. Patients who did have surgery showed significantly

less favorable scores on the sub-domain Physical Functioning on the SF-36 (64.1 ± 25.4 vs. 79.2 ± 19.4 , $p = .014$) compared to patients with no prior surgery. Additionally, they showed less favorable (=higher) scores on the sub-domain Behavioral Impairments on the NCSI (13.4 ± 16.0 vs. 8.7 ± 13.9 , $p = .039$). Patients with previous aortic dissection showed less favorable scores on the SF-36 sub-domains Physical Functioning (57.5 ± 21.4 vs. 77.4 ± 21.3 , $p = .006$), Social Functioning (62.8 ± 18.8 vs. 78.6 ± 22.1 , $p = .019$), and Bodily Pain (62.8 ± 18.8 vs. 78.6 ± 22.1 , $p = .019$).

3.4 | Coping styles

Male and female scores on the ADIQ were compared for the use of different coping styles. Males scored significantly higher on the coping style denial than females (2.75 [IQR 2.00 – 3.25] vs. 2.25 [IQR 1.75 – 3.25], $p = .018$). High scores on the subscale disease acceptance were present in 38 (49.4%) of males and 23 (35.4%) of females ($p = .094$). However, a false view of acceptance might be presented if patients who have high denial as well as high acceptance are included in this analysis. Therefore, we additionally performed analyses for patients with ‘true acceptance’, who showed a high score on the coping style acceptance without a high score on denial. This led to a true acceptance rate of 22 (28.6%) in males and 16 (24.6%) in females ($p = .596$). Table 4 shows differences in scores on all sub-domains of the three HRQOL questionnaires between patients with high acceptance or true acceptance, and patients without. Differences in baseline characteristics between patients with and without true acceptance were assessed. Patients with true acceptance were significantly younger (38.1 ± 15.1 vs. 43.5 ± 14.5 , $p = .044$), used beta blockers significantly more often (78.9% vs. 59.6%, $p = .033$), and significantly more often had a genetically confirmed *FBN1* mutation (97.3% vs. 83.2%, $p = .029$). Multivariate analysis showed significant associations between acceptance and the following baseline characteristics and NCSI sub-domains after correction for sex and age: hypertension ($p = .001$), current beta blocker use ($p = .008$), and angiotensin receptor blocker (ARB) use ($p = .003$).

TABLE 2 SF-36 scores: comparison of HTAD males and females to the general population

SF-36 subdomain	Males HTAD (n = 40)	Males general population	p-value	Females HTAD (n = 36)	Females general population	p-value
Physical functioning	81.4 ± 18.7	85.4 ± 21.0	.181	67.5 ± 23.8	80.4 ± 24.2	.003
Role physical	68.1 ± 39.2	78.7 ± 34.1	.096	58.3 ± 45.1	73.8 ± 38.5	.047
Bodily pain	79.1 ± 22.4	77.3 ± 22.7	.609	73.5 ± 22.0	71.9 ± 23.8	.658
General health	54.5 ± 18.8	71.6 ± 20.6	<.001	49.4 ± 24.3	69.9 ± 20.6	<.001
Vitality	58.3 ± 20.4	71.9 ± 18.3	<.001	57.8 ± 21.3	64.3 ± 19.7	.075
Social functioning	79.1 ± 22.4	86.0 ± 21.1	.059	73.5 ± 22.0	82.0 ± 23.5	.027
Role emotional	80.8 ± 36.1	85.5 ± 29.9	.419	81.5 ± 33.3	78.5 ± 35.7	.594
Mental health	74.0 ± 18.2	79.3 ± 16.4	.074	73.6 ± 18.3	73.7 ± 18.2	.963

Data are expressed as $M \pm SD$.

Abbreviations: HTAD, Hereditary Thoracic Aortic Disease; SF-36, Short Form 36 questionnaire.

3.5 | Baseline characteristics associated with HRQOL in MFS patients

HTAD patients who were employed showed significantly lower scores (indicating a better quality of life) on seven out of eight NCSI sub-domains, compared to HTAD patients who were not employed. One sub-domain (General Quality of Life) was borderline significant ($p = .053$). This analysis was done for the whole cohort (all ages), but the difference was even more pronounced when only HTAD of working age (18–65 years old, $n = 129$) were included in the analysis. No differences could be found for any of the baseline variables between HTAD patients of working age (18–65 years old) with and without employment. Except patients with employment had significantly less hyperlipidemia than those without (21.6% vs. 4.8%, $p = .005$).

Multivariate analysis showed significant associations with the following baseline characteristics and NCSI sub-domains after correction for sex and age. Employment was associated with more favorable scores on 5/8 NCSI sub-domains: Health-Related Quality of Life; Subjective Impairments; Behavioral Impairments; Subjective Symptoms; and Fatigue Symptoms. Hypertension was significantly associated with less favorable scores on: General Quality of Life; Health-Related Quality of Life; Subjective Impairments and Emotions about Symptoms. Larger aortic root diameter was significantly associated with less favorable scores on Subjective Symptoms. Having a partner was significantly associated with better scores on Satisfaction Relationships. Smoking was associated with less favorable General Quality of Life score. Sex was not significantly associated with scores on any sub-domain of the NCSI.

4 | DISCUSSION

To our knowledge, this is the first study to evaluate male–female-specific aspects, and male–female differences in HRQOL in HTAD patients. Very few studies have previously evaluated coping styles in these patients. We found both male and female HTAD patients had lower HRQOL compared to the general population. In female HTAD patients, physical well-being and behavioral functioning seemed most affected. Disease acceptance was comparable in male and female HTAD patients, while males scored significantly higher on the coping style ‘denial’. Disease acceptance was found to be independently associated with medication use and absence of hypertension. Although HRQOL was lower in females, we could not identify any factors associated with HRQOL specifically for either for males or females that could explain this difference. However, employment and disease acceptance were strongly associated with better HRQOL in both males and females.

Compared to the general Dutch population, both male and female HTAD patients scored lower on almost all SF-36 sub-domains. These findings are in accordance with the findings of studies in HTAD patients and patients with MFS, including children and young adults, which equally showed a reduced HRQOL compared to the

general population (Goldfinger et al., 2017; Handisides et al., 2019; Olsson & Franco-Cereceda, 2013; Rand-Hendriksen et al., 2010; Schoormans et al., 2012). This in contrast to adults with congenital heart disease, who were found to report a better HRQOL than the general population (Moons et al., 2006; Opic et al., 2015). Females predominantly reported problems on physical rather than mental aspect shown by significantly lower scores on 3/4 sub-domains of the PCS (Table 2). Remarkably, both male and female HTAD patients did not show lower scores on Bodily Pain when compared to the general population. This indicates that it might not be pain or discomfort causing lower scores on physical well-being, but caused instead by physical disabilities.

In our study, females showed more unfavorable scores on all three HRQOL questionnaires than males, which was also observed in the general Dutch population and other specific patient groups (Aaronson et al., 1998). This male–female difference was significant for: Behavioral Impairments (NCSI) and Physical Functioning (SF-36). These two sub-domains on the NCSI and SF-36 questionnaires have been compared previously, and were found to correlate well ($R = .71$; van Loenhout et al., 2013). Moreover, females scored significantly lower on the PCS of the SF-36. On the other hand, there was no significant difference between males and females for any of the baseline characteristics, including systemic score of MFS (according to the revised Ghent criteria) and previous aortic surgery or dissection (Loeys et al., 2010). It seems therefore that females were not more physically affected by the disease than males. Potentially this drop in self-reported physical well-being can be explained by the physical disabilities and limitations that HTAD patients experience in daily life, rather than the presence of pain or symptoms themselves.

We found a non-significant slightly higher prevalence of anxiety in females compared to males. A higher prevalence of anxiety in females compared to males was also found in the general population (Angst et al., 2002; Bijl, Ravelli, & van Zessen, 1998). In female HTAD patients, however, prevalence of anxiety seems to be markedly higher than in the general Dutch population (36.7% vs. 19.3%; Bijl et al., 1998). Surprisingly, the HADS outcomes showed a non-significant higher prevalence of depression in male HTAD patients compared to females. This is inconsistent with epidemiological studies which demonstrate a higher prevalence of depression in females compared to males. Although the prevalence is comparable to the general Dutch population where the prevalence of mood disorders was reported to be about 19% (Bijl et al., 1998). On the other hand, this is much lower than the rate of 44% depression previously reported in MFS (Peters, Kong, Horne, Francomano, & Biesecker, 2001), although this was measured using a different questionnaire for assessment of depressive symptoms.

HTAD patients with high scores on disease acceptance showed significantly better scores on almost all sub-domains, including lower scores on the HADS anxiety and depression subscales, which overall represents a better HRQOL. Males showed significantly higher scores on denial than females. Denial has been associated with lower distress (Carver et al., 1993). Theoretically, this might contribute to males showing better scores on HRQOL and less anxiety. Even

TABLE 3 HTAD male–female differences in scores on NCSI, SF-36, and HADS sub-domains

	Males (<i>n</i> = 77)	Females (<i>n</i> = 65)	<i>p</i> -value
NCSI (total score range)	<i>n</i> = 77	<i>n</i> = 65	
General Quality of Life (1–101.6)	15.0 (7.5–25.6)	15.4 (5.0–24.9)	.336
Health-related Quality of Life (2–10)	4.0 (3.0–6.0)	4.0 (2.0–6.0)	.821
Satisfaction Relationships (2–10)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	.350
Subjective Impairments (4–28)	10.1 ± 6.0	11.3 ± 6.1	.246
Behavioral Impairments (0–135.5)	0.0 (0.0–11.1)	8.8 (0.0–19.3)	.013
Subjective Symptoms (2–20)	8.6 ± 5.2	9.3 ± 4.7	.246
Emotions about Symptoms (6–24)	9.0 (7.0–12.0)	9.0 (8.0–12.0)	.566
Fatigue Symptoms (8–56)	33.9 ± 13.0	35.7 ± 13.6	.438
SF-36	<i>n</i> = 40	<i>n</i> = 36	
Physical Functioning	90.0 (70.0–95.0)	75.0 (55.0–83.8)	.005
Role Physical	87.5 (25.0–100.0)	75.0 (0.0–100.0)	.331
Bodily Pain	90.0 (67.5–100.0)	68.8 (60.0–97.5)	.268
General Health	54.5 ± 18.8	49.4 ± 24.3	.312
Vitality	58.3 ± 20.4	57.8 ± 21.3	.922
Social Functioning	90 (67.5–100.0)	68.8 (60.0–97.5)	.268
Role Emotional	100.0 (75.0–100.0)	100.0 (66.7–100.0)	.898
Mental health	74.0 ± 18.2	73.6 ± 18.3	.916
PCS	49.3 [42.3–54.6]	41.6 [35.5–53.1]	.035
MCS	50.5 (44.4–55.5)	52.4 [44.5–56.2]	.411
HADS	<i>n</i> = 64	<i>n</i> = 49	
Anxiety score	5.0 (2.3–8.0)	6.0 (2.0–9.0)	.623
Depression score	4.0 (2.0–7.0)	3.0 (1.0–6.0)	.251
Total score	9.5 (5.0–15.0)	9.0 (4.5–15.0)	.814

Note: Data are expressed as *M* ± *SD* when parametrically distributed or as medians (IQR) when non-parametrically distributed. Every NCSI sub-domain has its own specific score range, displayed as: sub-domain (total score range).

Abbreviations: NCSI, Nijmegen Clinical Screening Instrument; SF-36, Short Form 36; HADS, Hospital Anxiety and Depression Scale; PCS, Physical Component Summary; MCS, Mental Component Summary.

though males show higher denial, the true acceptance rate corrected for denial was not significantly different between males and females. Disease acceptance in our HTAD population was markedly lower than the 54%–65% previously reported (Connors et al., 2015; Van Tongerloo & De Paepe, 1998). This could be caused by the lack of a gold standard for measuring coping styles, which leads to the use of different measurement methods. In this study, we have used the ADIQ questionnaire, whereas previous studies have used the 'Utrechtse Coping Lijst' and 'The Coping Orientation to Problems Experienced inventory (COPE)' (Connors et al., 2015; Van Tongerloo & De Paepe, 1998). Furthermore, one study used the old Ghent Criteria for the diagnosis of MFS for inclusion of patients, and additionally included much younger patients (mean age 22.6 ± 4.8 years; Van Tongerloo & De Paepe, 1998). Moreover, these studies all have very small sample sizes, which might contribute to the variation in findings. More importantly, disease acceptance is known to be an important factor in relation to patients' adherence to treatment (Connors et al., 2015; Jankowska-Polanska et al., 2016). HTAD

patients are always under long-term surveillance, receive counseling on lifestyle modifications (e.g. exercise, smoking) and are often prescribed medication. Beta blocker and ARB use were found to be positively associated with acceptance, and hypertension was negatively associated with acceptance. Furthermore, hypertension was associated with less favorable scores on the NCSI, indicating more problems and lower HRQOL. This strengthens the assumption that disease acceptance improves patients' adherence to medical treatment, with adherent patients having less hypertension. Our results emphasize that coping style, and especially disease acceptance, is underexposed, but truly important in the management of HTAD patients. These findings correspond with a previous study showing that bio-behavioral factors play a big role in quality of life of MFS patients (Moon et al., 2016).

Employment seems to be a very important factor in HRQOL of patients with MFS. It is striking that the association with such daily life aspects seems so strong, whereas medical- and disease-related factors such as aortic root diameter, previous surgery, family history,

TABLE 4 Comparison of NCSI, SF-36, and HADS sub-domain scores in HTAD participants with and without disease acceptance/true disease acceptance

	Acceptance (n = 61)	No acceptance (n = 81)	p-value
NCSI	n = 61	n = 81	
General Quality of Life (1–101.6)	9.4 (4.0–15.2)	20.7 (11.5–37.1)	<.001
Health-Related Quality of Life (2–10)	3.0 (2.0–4.0)	5.0 (4.0–7.0)	<.001
Satisfaction Relationships (2–10)	3.0 (2.0–3.5)	4.0 (2.0–5.0)	.147
Subjective Impairments (4–28)	7.0 (4.0–10.0)	12.0 (8.0–17.0)	<.001
Behavioral Impairments (0–135.5)	0.0 (0.0–7.0)	9.8 (0.0–19.9)	<.001
Subjective Symptoms (2–20)	6.5 (3.0–12.0)	10.00 (6.00–14.00)	.001
Emotions about Symptoms (6–24)	8.00 (7.0–10.3)	10.00 (8.00–13.00)	.005
Fatigue symptoms (8–56)	29.0 (12.4)	39.1 (12.3)	<.001
SF-36	n = 35	n = 41	
Physical Functioning	85.0 (75.0–95.0)	75.0 (57.5–90.0)	.068
Role Physical	100.0 (75.0–100.0)	50.0 (0.0–100.0)	.002
Bodily Pain	89.8 (67.4–100.0)	67.4 (44.9–89.8)	.010
General Health	54.3 (12.7)	52.7 (12.7)	<.001
Vitality	70.7 (15.5)	52.2 (19.2)	<.001
Social Functioning	100.0 (87.5–100.0)	75.0 (62.5–87.5)	<.001
Role Emotional	100.0 (100.0–100.0)	100.0 (33.3–100.0)	.016
Mental health	60.0 (56.0–64.0)	56.0 (52.0–60.0)	.153
HADS	n = 46	n = 67	
Anxiety score	4.0 (3.3)	7.1 (4.4)	<.001
Depression score	2.8 (2.5)	6.1 (4.8)	<.001
Total score	6.8 (5.1)	13.3 (8.3)	<.001
	True acceptance (n = 38)	No true acceptance (n = 104)	p-value
NCSI	n = 38	n = 104	
General Quality of Life (1–101.6)	6.0 (3.0–14.6)	17.7 (8.1–31.0)	<.001
Health-related Quality of Life (2–10)	3.0 (2.00–4.3)	5.0 (3.0–7.0)	<.001
Satisfaction Relationships (2–10)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	.322
Subjective Impairments (4–28)	7.0 (5.5–10.0)	10.5 (6.0–16.0)	.003
Behavioral Impairments (0–135.5)	0.0 (0.0–8.5)	5.4 (0.0–18.2)	.010
Subjective Symptoms (2–20)	5.0 (3.0–12.3)	10.0 (6.0–14.0)	.006
Emotions about Symptoms (6–24)	8.0 (6.8–9.3)	10.0 (8.0–13.0)	.008
Fatigue Symptoms (8–56)	29.6 (12.3)	36.6 (13.2)	.005
SF-36	n = 24	n = 52	
Physical Functioning	80.0 (71.3–93.8)	80.0 (60.0–93.8)	.500
Role Physical	87.5 (56.3–100.0)	75.0 (0.0–100.0)	.247
Bodily Pain	89.8 (67.4–97.5)	77.6 (57.1–100.0)	.409
General Health	55.0 (12.9)	52.7 (12.5)	.462
Vitality	70.4 (15.0)	56.3 (20.3)	.003
Social Functioning	100.0 (87.5–100.0)	75.0 (62.5–100.0)	.00
Role Emotional	100.0 (100.0–100.0)	100.0 (33.3–100.0)	.131
Mental health	60.0 (56.0–64.0)	60.0 (52.0–60.0)	.154
HADS	n = 28	n = 85	
Anxiety score	4.32 (3.44)	6.39 (4.37)	.025
Depression score	2.64 (2.11)	5.45 (4.61)	<.001
Total score	6.96 (4.69)	11.84 (8.31)	<.001

Note: Data are expressed as mean with SD when parametrically distributed or as medians (IQR) when non-parametrically distributed.

Abbreviations: HTAD, hereditary thoracic aortic diseases; NCSI, Nijmegen Clinical Screening Instrument; SF-36, Short Form 36; HADS, Hospital Anxiety and Depression Scale.

and previous aortic dissection showed almost no association with HRQOL. These findings are very similar to the findings of the largest HRQOL in HTAD patients performed so far by Goldfinger et al. (2017) and Moon et al. (2016). Similar findings were also reported in a very recent study in children and adolescents with MFS (Handisides et al., 2019). No explanation could be found from the differences in baseline variables between HTAD patients of working age with and without employment. Nonetheless, employment is influenced by many factors: disease-related factors, daily life aspects (also bio-behavioral factors), and demographic factors. In turn, employment has consequences on many factors as well, mainly social support and daily life aspects (independence, self-worth, family life, and social life). The connection between employment and all these different factors might explain its strong association with HRQOL and makes it an important factor to consider when counseling HTAD patients.

Even though no association between previous aortic dissection and HRQOL scores on the NCSI could be found, patients with previous aortic dissection scored lower on most SF-36 sub-domains. This was especially prominent in the PCS. Patients who previously underwent aortic surgery showed significantly lower scores on the sub-domain Physical Functioning, but overall seemed to show less prominent reduction in HRQOL. When interpreting these findings, it is important to keep in mind that the SF-36 was only completed by a subset of our cohort ($n = 76$), which could explain why no statistically significant difference was detected.

4.1 | Clinical implications

The findings of this study should lead to more awareness among patients, families, and healthcare providers such as clinical geneticists, genetic counselors, cardiologists, and psychologists about the impact aortic disease has on the patients' HRQOL. In genetic counseling as well as cardiovascular treatment of HTAD patients, HRQOL assessment should be incorporated, since this is crucial in order to provide the counseling and guidance needed for HTAD patients and their families. Additionally, we identified several factors which influence HRQOL in HTAD patients, which are valuable leads for counseling. We found that disease-related factors appear less important for HRQOL in HTAD patients than daily life aspects and coping style, which seems to positively influence HRQOL, and patients' adherence to medical treatment. It has been mentioned before that subjective perception of the diagnosis may be an important factor influencing HRQOL (Velvin, Wilhelmsen, Johansen, Bathen, & Geirdal, 2019). Therefore, interventions aimed at modifying coping strategy and other daily life aspects should be considered. The first step toward this can be made by incorporating patient-reported quality of life into clinical practice, in order to select the patients who need extra counseling and guidance.

4.2 | Limitations

This study has some limitations. Most importantly, the SF-36 and HADS questionnaires were not completed by all participants. This

was due to logistic issues, because of which the SF-36 and HADS questionnaires could not be distributed during a certain period of time. Therefore, we do expect the distribution of the completed SF-36 and HADS questionnaires over our study population to be random. No significant difference was found between the percentage of males and females who completed the SF-36 and HADS questionnaires. Patients who completed the SF-36 had significantly larger aortic root diameters than those who did not. However, no associations were found between aortic root diameter and HRQOL. Furthermore, no significant difference in scores on any of the NCSI questionnaire sub-domains was found between patients who did, and those who did not complete the SF-36 questionnaire. There was no difference in HRQOL measurements between those two groups, since the NCSI sub-domains were found to correlate well with the SF-36 sub-domains (van Loenhout et al., 2013). It seems therefore that the subset of HTAD patients who completed the SF-36 and HADS questionnaires was representative of our total study population. Unfortunately, with the NCSI no comparison with the general population could be made. Therefore, our comparison between HTAD patients and the general Dutch population is limited. Furthermore, the response rate to the questionnaires was 47.1%, which is comparable to other online surveys (Ebert, Huibers, Christensen, & Christensen, 2018). Finally, our study population contained many patients diagnosed with MFS ($n = 123$). However, baseline characteristics for patients with and without MFS seemed comparable (Supporting Information S2). Therefore, all participants were included in analysis comparing HTAD patients to the general population and comparing males and females. For studying associations between HRQOL and baseline characteristics only the patients with MFS were included.

5 | CONCLUSIONS

HTAD patients showed subnormal HRQOL. Females reported markedly lower HRQOL compared to males and females in the general population, predominantly on physical well-being. Disease acceptance was associated with better HRQOL and patients' adherence to treatment. Interestingly, factors such as employment, coping style, and disease acceptance seem more important for HRQOL than disease-related factors. These findings offer valuable leads for counseling and guidance of both male and female HTAD patients.

AUTHOR CONTRIBUTIONS

Carlijn Thijssen provided substantial contributions to the conception, design, data collection, data analysis, interpretation of the data, and preparation of the manuscript. Roland van Kimmenade co-supervised this project from its conception, including the study design, data analysis and interpretation, and manuscript preparation. These authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Daphne Doze, Arjen Gökalp, Janneke Timmermans, Jeannette Peters, Laura Elbers,

Niels van Royen, Johanna Takkenberg, and Jolien Roos-Hesselink provided substantial contributions to the conception, design, and drafting of this work, aided in revising the work critically for important intellectual content, and provided final approval of the version to be published. All authors consented to the submission of this manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

Authors Carlijn G.E. Thijssen, Daphne E. Doze, Arjen L. Gökalp, Janneke Timmermans, Jeannette B. Peters, Laura H.C. Elbers-van de Ven, Niels van Royen, Johanna J.M. Takkenberg, Jolien W. Roos-Hesselink, and Roland R.J. van Kimmenade declare that they have no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (RRJvK) upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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